Claims

1. A method of introducing at least one functional human cytochrome P450 into non-human cell(s) whose own endogenous P450s have been rendered inactive, the method comprising introducing DNA encoding said at least one human P450 such that said human P450 remains functional where the cell's own endogenous P450s are inactive.

2. A method according to claim 1 wherein the non-human cell's own endogenous P450s are rendered inactive by deletion of the endogenous CPR gene and where function of the at least one introduced human cytochrome P450 is maintained either by it being in modified form such that it can function independently of any separate CPR protein or by introducing into the non-human cell DNA encoding a CPR such that said at least one introduced human P450 can function in the non-human animal cell(s).

3. A method according to either preceding claim wherein the non-human cell(s) is/are derived from a monkey, dog, cat, rabbit, hamster, rat, or mouse.

4 A method according to claim 3 wherein the non-human cell(s) is/are derived from a mouse.

5. A method according to any preceding claim wherein a plurality of DNA sequences encoding different human cytochrome P540s are introduced into the non-human cell(s).

6. A method according to any preceding claim wherein the human cytochrome P450 is selected from the group comprising 3A4, 2D6, 2C9, 1A2, 2C19 and 2C8.

7. A method according to any preceding claim wherein expression of the human cytochrome P450 as either, part of a cytochrome P450-cytochrome P450 reductase fusion protein or co-expression of the human cytochrome P450 with a separate cytochrome P450 reductase, results in enzymatically active human P450 enzymes.

8. A method according to any preceding claim wherein expression of the human cytochrome P450 as either, part of a cytochrome P450-cytochrome P450 reductase fusion protein or co-expression of the human cytochrome P450 with a separate cytochrome P450 reductase are driven by a gene promoter.

9. A method according to claim 7 wherein the promoter is CMV or a tissue-specific rat albumin promoter or CYP1A1.

10. A method according to any one of claims 6 to 9 wherein expression of the fusion protein or separate human cytochrome P450 and P450 reductase fusion proteins is/are constitutive or conditional.

11. A method according to any of claims 6 to 10 wherein the fusion protein or separate human cytochrome P450 and P450 reductase fusion proteins is/are targeted to a specific cellular component where non-human animal P540s are not expressed.

12. A method according to any preceding claim wherein an intracellular targeting sequence is added to the fusion protein or separate human cytochrome P450 and P450 reductase fusion proteins.

13. A method according to any preceding claim further including the step of introducing at least one further DNA sequence encoding a human protein/enzyme other than a P450 that is involved in xenobiotic metabolism.

14. A method according to claim 13 wherein the at least one further DNA sequence encoding a human protein encodes a drug transporter protein.

15. A method according to claim 14 wherein the DNA sequence encoding a human protein encodes Mdr.

16. Use of a transgenic animal, tissues and/or cells produced by the method according to any preceding claim that have been modified to contain and express DNA encoding at least one human P450 and/or another protein involved in metabolism so as to investigate human P450 mediated metabolism in said a transgenic animal, tissues and/or cells derived therefrom.

17. Use according to claim 16 in investigation disease states selected from the group comprising choleastasis, artherogenesis, hormonal imbalances, neurological disorders, degenerative diseases, skin conditions, cardiovascular disease, cancer and glaucoma and any other disease in which P450s play a role.

18. Use of human cells introduced into an immune-deprived reductase null animal so as to investigate contribution of said human cells in P450-mediated product metabolism and/or toxicity and/or drug candidate screening.

19. A method according to claim 18 wherein said human cells are hepatocytes.

20. A CYP3A4/CPR transgenic HRN™ mouse.

21. Use of a mouse according to claim 20 in pre-clinical and toxicity studies.